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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,955	02/06/2006	Gerd Haberhausen	21518-US	2633

22829 7590 03/27/2008

Roche Molecular Systems, Inc.
Patent Law Department
4300 Hacienda Drive
Pleasanton, CA 94588

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
03/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,955	HABERHAUSEN ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The preliminary amendment filed May 16, 2005 has been entered. The examiner acknowledges the amendment to the specification. Claim 1-10 are under consideration in this office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on June 3, 2005 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

3. Claim 1-10 are objected to because of the following informalities:

a) Claim 1 refers to gram positive pathogenic organisms and pathogenic gram positive bacteria. It is suggested that consistent terminology, such as pathogenic gram positive bacteria be used throughout the claims.

b) Dependant claims 2-9 refer to "A method according to claim 1", however the suggested claim language is to use of the article "The." Therefore the suggested claim language is "The method according to claim 1"

c) Claims 4-5 and 10 do not italicized the genus species names of *Staphylococcus aureus Streptococcus pneumoniae, Enterococcus faecium* and *Enterococcus faecalis.*

d) Claim 5 misspells *pneumoniae* as "preumoniae". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like FRET must be spelled out when used for the first time in a chain of claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-2 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/534,915 in view of Jannes et al., (WO96/00298 published January 1996). Although the conflicting claims are not identical, they are not patentably distinct from each other because

While these claims are not identical, they are not patentably distinct from one another. The claims of 10/534,915 are directed to a more narrow method of amplification and detection of pathogenic organisms comprising detection of a specific rRNA spacer region. While application 10/534,955 does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23 S rRNA sequences. The claims of 10/534,955 application are directed to a method for identification of a Gram positive pathogenic organism comprising amplification of a clinical sample, detecting amplification through hybridization, monitoring hybridization and identifying the organism(s). Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in both applications. Furthermore, in the instant application,

gram positive bacteria are detected, however the method of 10/534,915 comprises the identification of any pathogenic organism, including pathogenic gram positive bacteria. The similarities between these two copending applications, including the steps of monitoring temperature dependence of hybridization and using this hybridization detection to identify specific organisms, render the method of the instant application obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

6. Claims 1, 4 and 8-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of copending Application No. 10/532,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because

While these claims are not identical, they are not patentably distinct from one another. The claims of the copending '319 application are directed to a method for detecting the presence of bacterial pathogens in clinical samples, comprising steps directed to the isolation of nucleic acids, amplification and quantifying the amount of nucleic acids comprising a sequence that is specific for a bacterial pathogen, wherein the method of quantification comprises amplification, monitoring of amplification through a hybridization probe and through monitoring temperature dependence of hybridization. The claims of the instant application are directed to a method for identification of a

Gram positive pathogenic organism comprising amplification of a clinical sample, detecting amplification through hybridization, monitoring hybridization and identifying the organisms. The differences between the instant application and the 10/532,319 application lie in the specific recitation of analysis of clinical samples and comprising the use of hybridization reagents with the real-time monitoring of amplification, which falls within the scope of the amplification, detection and monitoring of temperature dependence of hybridization in the instant application.

The similarities between these two copending applications, including the steps of monitoring temperature dependence of hybridization and using this hybridization detection to identify specific organisms, render the method of the instant application obvious.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Jannes et al., (WO 96/00298).

Claim 10 is drawn to a kit for the identification of a Gram positive pathogenic bacterium selected from the genera *Enterococcus, Staphylococcus* and *Streptococcus* containing a set of primers capable of amplifying a sequence of at least 20 nucleotides from the 16S-23S rRNA spacer region of *Enterococcus, Staphylococcus* or *Streptococcus*.

Jannes et al., teach kits for detection of at least one organism in a sample were primers are used which enable the detection of a particular panel of organisms selected from the genera *Staphylococcus, Enterococcus* and *Streptococcus* (page 5, lines 13-24). Jannes et al., teach new sequences of 16S-23S rRNA spacer regions to derive useful primers (page 5, lines 11-12). Jannes et al., also teach primers as specified in Table 1b.

Therefore Jannes et al., teach the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jannes et al., (WO 96/00298) in view of de Silva et al., (Biochemica. 1998. No. 2:12-15).

Claim 1 is drawn to a method for identification of a Gram positive pathogenic organism or a subset of organisms being a member of a predetermined group of pathogenic Gram positive bacteria in a clinical sample comprising: a) providing a clinical specimen containing at least partially purified nucleic acid, b) subjecting said clinical specimen to at least one amplification step and at least one detection step, said steps comprising ba) an amplification step using at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence region from a predetermined sub-group of pathogenic Gram positive bacteria to which said Gram positive pathogenic organism belongs, bb) a detection step using at least one hybridization reagent capable of detecting said pre-selected nucleic acid sequence region from said predetermined sub-group of pathogenic Gram positive bacteria, said detection step bb) further comprising bba) monitoring hybridization at a pre-selected temperature, said hybridization being indicative for the presence in the sample of at least one species contained in said sub-group, and bbb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for the presence of at least the species of said pathogenic Gram positive bacterium or said subset of organisms, c) identifying said organism or said subset of organisms based on the results of the monitoring steps in bb).

Claim 2 is drawn to the sub-group being a genus. Claim 3 is drawn to the hybridization reagent comprises two probes complementary to adjacent sequences in the target nucleic acid sequence region, one being labeled by a FRET donor, and the other being labeled by a FRET acceptor. Claim 4 is drawn to the predetermined group

of pathogenic Gram positive bacteria comprising the species *Staphylococcus aureus* and coagulase-negative staphococci. Claim 5 is drawn to the predetermined subgroup comprising the species *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecium* and *Enterococcus faecalis*. Claim 6 is drawn to the preselected nucleic acid sequence region comprising at least 20 nucleotides of an rRNA spacer region. Claim 7 is drawn to the amplification and detection steps being performed homogeneously. Claim 8 is drawn to the species being selected from the genera *Staphylococcus, Enterococcus* and *Streptococcus*. Claim 9 is drawn to the species being selected from the genus *Staphylococcus*.

Jannes et al., teach a method of amplification and detection of one or several pathogenic organisms, specifically bacteria, through the detection of the rRNA spacer region (abstract). Jannes teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising:
a) at least partially purifying nucleic acid from a clinical sample (Example 3, p. 78-83; alternatively, see Example 4, p. 84-86, p. 85 where clinical isolates were tested, see Table 7), b) subjecting said clinical specimen to at least one amplification step and at least one detection step, comprising: ba) an amplification step using at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising region from a predetermined sub-group of pathogenic Gram-positive bacteria to which said gram positive pathogenic bacteria belong (p. 82-83 or p. 85, bb) a detection step using at least one hybridization reagent capable of detecting a pre-selected nucleic acid sequence region from said sub-group of pathogens (p. 82-83 or p.

85, where clinical isolates were amplified using biotinylated primers and hybridized to 16s/23s rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or 7 for hybridization results), said detection step bb) further comprising: bba) monitoring hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for the presence in the sample of at least one species contained in the sub-group (p. 82-83 or p. 85, where clinical isolates were amplified and hybridized to 16s/23s rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or Table 7, where a variety of pathogens within a group were distinguished), and identifying the organisms or subset of organisms based on the results of step bb).

Jannes et al., teach clinical samples such as ones originating from the respiratory tract, cerebrospinal fluid, urogential tract, gastro-intestinal tract and food and environmental samples (pages 3-4, lines 24-7). Jannes et al., teach a method of detection and identification of particular taxons, genus, subgroups, species, subtypes, serovars and the like (page 4, lines 7-11). Jannes et al., teach a rRNA spacer region that is at least 20 nucleotides present in one or multiple copies of almost all eubacterial organism (page 2, lines 12-15).). Jannes et al., teach the identification of *Listeria, Mycobacterium, Streptococcus, Staphylococcus aureus* (page 4, lines 11-24 and page 5, lines 2-3). Jannes et al., teach an embodiment wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, Example 3, p. 78, where *Listeria*, a gram positive organism is detected. Jannes et al., teach the use of a predetermined group including *Staphylococcus aureus, Streptococcus pneumoniae* (page 24, lines 1-7; page 25, lines 1-7). Table 6 shows

predetermined groups having *Enterococcus faecalis* and *Enterococcus faecium*. Example 9 and Table 9 show taxa tested. However, Jannes et al., do not explicitly teach step bbb, wherein the temperature dependence of hybridization is monitored as indicative for at least the species of said pathogen.

de Silva et al., teach an embodiment comprising bbb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for at least the species of said pathogen (p. 14, Figures 3 and 5, where an example of monitoring temperature dependence of hybridization is depicted). de Silva et al., teach fluorescence monitoring of amplification using hybridization probes based upon signals generated by FRET offers advantages over other techniques because its linear responses over a large dynamic range (page 12). Once amplification and FRET occur, a melting curve is generated that allows for rapid genotyping (page 13). de Silva et al., teach continuous fluorescence monitoring of the reaction as temperature is raised (page 13). de Silva et al., teach that changes can be easily distinguished suggesting that the fluorescence method is suitable for all single base mismatches (page 13). de Silva et al., teach a sensitive system that allows a single template copy to be distinguished and fluorescent probes that obtain the strongest signals (page 14-15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the methods taught by Jannes et al., to incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva et al., to arrive at the claimed invention with a reasonable expectation for success. While Jannes et al., teach

standard hybridization and detection of pathogenic sequences, it would have been *prima facie* obvious in view of the teachings of de Silva to monitor amplification using melting curve analysis to establish melting temperature as claimed and potentially to apply the sequence specific line probes used for detection of the rRNA spacer sequences to the fluorescent FRET format of amplification and detection. Furthermore, there is a reasonable expectation of success in incorporating the methods of Jannes et al., and de Silva et al., since de Silva et al., teach sequence specific monitoring of PCR products is routinely performed by hybridization analysis using other are time-consuming methods which involve several handling steps that increase the risk of end-product contamination and sample tracking errors, however de Silva teach more dynamic results using rapid-cycle PCR with real-time fluorescence monitoring which allows high throughput genotyping and product quantification. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Jannes et al., and incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva to arrive at the claimed invention with in order to provide a more sensitive system having stronger signals.

Conclusion

9. No claims allowed.

10. . Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/

Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645